Declaration regarding US Application Serial No. 10/627,483

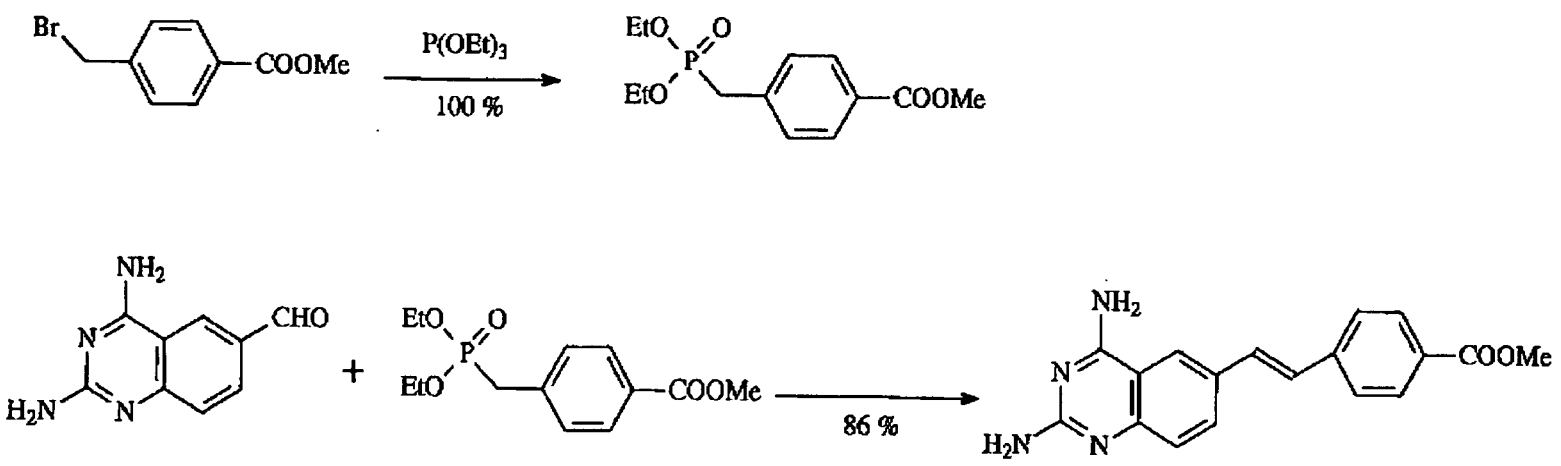
I, Harry Kochat, do hereby state that all statements made of my own knowledge are true and that all statements made on information and belief are believed to be true.

I am the Head, Chemistry Drug Discovery & Senior Manager, CMC Operations at BioNumerik Pharmaceuticals, Inc., the assignee of the above application, and a co-inventor in the above-entitled application. I have held the position of Head, Chemistry Drug Discovery & Senior Manager, CMC Operations at BioNumerik Pharmaceuticals, Inc. for the past 12 years, prior to that I worked as Senior Research Investigator at Rice University, Houston, Texas. I hold a Ph.D. in Organic Chemistry through an international exchange program between Malti-Chem Research Center, India and Purdue University, West Lafayette, Indiana, USA. I have reviewed the Final Rejection issued by the Examiner on 3/30/2005 in the above matter, as well as the references cited by the Examiner, the application itself, and the proposed claims and remarks prepared by BioNumerik's attorney in response to this Final Rejection.

The proposed claims relate to a process for synthesizing TRIDAM and certain analogues, derivatives and/or congeners thereof. The Examiner has noted that the House reference, which, according to the Examiner, teaches "that phosphonate compounds, which are derived from triethyl phosphate, are 'a modification of the Wittig reaction... which has proved of value.'" Nevertheless, none of the cited references teach or in any way suggest such a "modified Wittig reaction" applied to a pteridine moiety or a quinazoline moiety and its application in the synthesis of MDAM, L-MDAM, M-TREX and similar antifolates compounds that have C_C bridging between the central aromatic core with the pteridine moiety.

Moreover, results from the known, conventional Wittig process (based on results from the literature) for antifolate synthesis, are as shown below:

The "modified Wittig reaction" used in synthesis of antifolates is shown below:



In comparison to the conventional Wittig reaction above, the modified Wittig reaction greatly increased the overall yield of the process (73% to 86%), as shown.

In addition, our modified Wittig reaction permits more efficient isolation of the final product. One of the biggest drawbacks of Wittig reaction is the difficulty of removing the byproduct of *in-situ* generated stoichometric amount of triphenylphospine oxide. This technical difficulty is eliminated in our improved process by substituting dimethylphosphonate as the phosphorus reagent. The byproduct of dimethylphosphonate in our improved process can be very easily removed by washing with water. Not only was the yield lower (73%) where the conventional Wittig reaction was used, but the olefinic Wittig product generated was reported as contaminated with phosphine oxide by-product. In order to get reasonably pure product, the Wittig product needs to undergo a repeated and tedious crystallization process. Repeated crystallization could lower the yield of the reaction further.

In conclusion, the modified Wittig reaction provides considerable advantages over the conventional process for the synthesis of antifolates and their analogues, and this was not disclosed or suggested in the prior art.

I hereby state that willful false statements and the like are punishable by fine or imprisonment, or both (18 USC 1001) and may jeopardize the validity of the application or any patent issuing thereon.

Henry Huckert

Date 6/15/2005